Remarks

Claims 1-43, 65, and 66 are pending in this application. Claims 3, 5-7, 9, 11, 14-16, 19, 21, 24, 26-28, 30, 32, 35-37, 40, 42, and 44-64 have been withdrawn from consideration as unelected subject matter. Claims 44-64 have been canceled. Applicants reserve the right to file one or more continuing applications drawn to the subject matter of claims 44-64. Claims 18 and 39 have been amended. Claims 65 and 66 are new. Support for claims 18, 39, 65, and 66 is found, for example, at page 25, lines 8-15. No new matter was added to the application by virtue of these amendments. Applicants respectfully submit that these amendments place the application in condition for allowance or in better condition for appeal and, therefore, these amendments should be entered. Therefore, claims 1, 2, 4, 8, 10, 12, 13, 17, 18, 20, 22, 23, 25, 29, 31, 33, 34, 38, 39, 41, 43, 65, and 66 are currently under consideration.

The numbers of independent claims and total claims currently pending in the application do not exceed the numbers of such claims upon filing of this application. Therefore, no excess claims fees are due.

A Petition Under 37 C.F.R. § 1.136(a) for a three-month extension of time and the associated fee are enclosed with this paper.

I. <u>Response to Objection to Specification</u>

The specification was objected to for containing an embedded hyperlink or other form of browser-executable code. The specification has been amended at the paragraph beginning at page 20, line 1, for deleting the hyperlink or other form of browser-executable code. Withdrawal of the objection is respectfully requested.

No new matter is added to the application by virtue of this amendment.

In view of the above, withdrawal of the objection to the specification is respectfully requested.

II. <u>Response to Rejections Under 35 U.S.C. § 112, Second Paragraph</u>

Claims 18 and 39 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. More particularly, claims 18 and 39 were rejected for reciting the range "0.01-0.50." The Office Action alleged that this term is relative and indefinite.

Applicants respectfully submit that claims 18 and 39 as originally submitted are definite under 35 U.S.C. § 112, second

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paragraph. Nevertheless, to accelerate allowance of the application, these claims have been amended. In view of these amendments, the terminology alleged to be indefinite has been removed from the claims. Therefore, the rejection under Section 112, second paragraph, is obviated, and withdrawal of the rejection is respectfully requested.

III. Response to Rejections Under 35 U.S.C. § 103

    A.   Standards Under 35 U.S.C. § 103

A brief review of the parameters for examination under 35 U.S.C. § 103(a) was set out in the previous response. That review is hereby incorporated by reference.

In addition, Applicants respectfully submit that when obviousness is alleged based on the teachings of multiple references, some "suggestion, teaching, or motivation" must be established that would have led a person of ordinary skill in the art to combine the relevant teachings in the manner claimed. *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999); *Pro-Mold & Tool Co. v. Great Lakes Plastics Inc.*, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

> The reason, suggestion, or motivation to combine may be found explicitly or implicitly: 1) in the prior art references themselves; 2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references, are of special

interest or importance in the field; or 3) from the nature of the problem to be solved, "leading inventors to look to references relating to possible solutions to that problem." *Pro-Mold & Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1572, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996) (internal citations omitted); *In re Rouffet*, 149 F.3d at 1357, 47 USPQ2d at 1458.

Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000).

"[T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F3d, 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). This is because "[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." *Id.* Therefore, a person of ordinary skill in the art must not only have had some motivation to combine the prior art teachings, but some motivation to combine the prior art teachings in the particular manner claimed. *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317-18 (Fed. Cir. 2000) ("Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination *in the manner claimed*." (emphasis added)); *In re*

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Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998) ("In other words, the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination *in the manner claimed."* (emphasis added)).

B.   Argument

Claims 1, 2, 4, 8, 10, 12, 13, 17, 20, 22, 23, 25, 29, 31, 33, 34, 38, 41, and 43 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over O. Matveeva et al., Prediction of antisense oligonucleotide efficacy by in vitro methods, 16 Nature Biotechnology 1374-1375 (1998) ("Matveeva"), in view of Wu et al., Back-propagation and counter-propagation neural networks for phylogenetic classification of ribosomal RNA sequences, 22 Nucleic Acids Res. 4291-4299 (1994) ("Wu"). The rejection of claims 1, 2, 8, 10, 12, 17, 22, 23, 29, 31, 33, 38, and 43 under Section 103(a) has been maintained from the Office Action dated May 24, 2005. However, claims 4, 13, 20, 25, 34, and 41 were not previously rejected under Section 103(a). In other words, the rejection of claims 4, 13, 20, 25, 34, and 41 under 35 U.S.C. § 103(a) is new.

1. The Office Action failed to show each and every
    limitation of the claimed invention in the cited
    references.

In re Ehrreich, 200 USPQ 504, 509-11 (CCPA 1979), and more
recent Federal Circuit cases make clear that to establish a case
of *prima facie* obviousness, the USPTO must show all of the
limitations of the claimed invention in the prior art.

Matveeva discloses a statistical evaluation of the degree of
correlation between data of *in vitro* assays (*i.e.*, RNase H
mapping and gel-mobility shift assays) that measure C-*raf* mRNA
regional accessibility to complementary oligonucleotides and
levels of intracellular C-*raf* mRNA inhibition produced by those
oligonucleotides. Wu discloses a neural network for phylogenetic
classification by analyzing ribosomal RNA sequences for
structural similarities.

The combination of Matveeva and Wu fails to show each and
every limitation of any claim. For example, with respect to
claim 1 the combination of Matveeva and Wu fails to show at least
the following:

(1) mapping sequence motifs of a preselected length
found in the sequence data contained in the database,
entering counts for each of the sequence motifs in selected
input nodes of the input layer, and entering activity data
correlated with the counts of the sequence motifs;

(2) training the artificial neural network having the counts entered in the input layer such that the artificial neural network produces an output in the output layer upon entry of sequence motif counts, wherein the output comprises a measure of predicted activity correlated with sequence motif counts for a test oligonucleotide;

(3) mapping sequence motifs of the preselected length present in a nucleotide sequence of a test oligonucleotide complementary to at least a portion of the selected RNA, determining counts of the mapped sequence motifs, and entering counts of the sequence motifs present in the nucleotide sequence of the test oligonucleotide in the input layer of the artificial neural network, and

(4) obtaining output of the predicted antisense activity of the test oligonucleotide for down-regulating expression of the selected RNA.

Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the rejection is respectfully requested.

2. <u>The Office Action failed to establish a teaching, motivation, or suggestion in the prior art for combining the cited references in the manner claimed</u>.

The Federal Circuit has made clear that to establish a *prima facie* case of obviousness by combining references, the *prima facie* case must include a showing of a teaching, motivation, or suggestion in the prior art for combining the cited references in the manner claimed.

In the first place, the Office Action failed to show that Matveeva and Wu can be combined in the manner claimed. That is, as set forth above the Office Action failed to show that the combination of Matveeva and Wu contains each and every limitation found in the claims.

Still further, however, the Office Action failed to establish a teaching, motivation or suggestion for combining Matveeva and Wu in the manner claimed. The Office Action failed to show the required teaching, motivation, or suggestion (1) in the cited references themselves; (2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references, are of special interest or importance in the field; or (3) from the nature of the problem to be solved.

Matveeva discloses that prediction of antisense oligonucleotide efficiency by *in vitro* methods is a step toward

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being able to efficiently predict antisense activity in cells

using simplified model systems. Matveeva goes on to state that

additional data for other mRNAs must be obtained and analyzed

with statistical methods for the future practical use of such

assays. However, Applicants agree with the admission of the

Office Action that Matveeva does not teach or suggest a method of

using or making artificial neural networks for predicting the

activity of antisense oligonucleotides for down-regulating

expression of a selected RNA.

Wu teaches use of a neural network for classification of

ribosomal RNA sequences according to phylogenetic relationship.

That is, Wu teaches that neural networks are useful for analyzing

databases developed according to family relationships based on

structural similarities. Wu fails to teach or suggest, however,

analyzing databases according to functional similarities.

Therefore, Wu also fails to teach or suggest using or making

artificial neural networks for predicting the activity of

antisense oligonucleotides for down-regulating expression of a

selected RNA.

Hence, the Office Action failed to show the required

teaching, motivation, or suggestion for combining Matveeva and Wu

in the manner claimed. Thus, a *prima facie* case of obviousness

was not established, and withdrawal of the rejection under

Section 103(a) is respectfully requested.

      3.   <u>Absent a teaching, motivation, or sugggestion to combine the cited references, the Office Action inappropriately resorted to hindsight to reject the claims</u>.

"Combining prior art references without evidence of such a

suggestion, teaching, or motivation simply takes the inventor's

disclosure as a blueprint for piecing together the prior art to

defeat patentability—the essence of hindsight." *In re Dembiczak,*

supra. Applicants respectfully submit that absent a teaching,

motivation, or suggestion to combine the cited references, the

Office Action resorted to the inappropriate use of hindsight to

rejection the claims. As the court stated in *In re Carroll*, 202

U.S.P.Q. 571, 572 (C.C.P.A. 1979):

> One of the more difficult aspects of resolving
> questions of non-obviousness is the necessity "to guard
> against slipping into use of hindsight." Graham v.
> John Deere Co., 383 U.S. 1, 36, 148 USPQ 459, 474
> (1965). Many inventions may seem obvious to everyone
> after they have been made. However, 35 USC 103
> instructs us to inquire into whether the claimed
> invention "would have been obvious at the time the
> invention was made to a person having ordinary skill in
> the art to which said subject matter pertains." Thus,
> in deciding the issue of obviousness, we must look at
> the prior art presented from a vantage point in time
> prior to when the invention was made, and through the
> eyes of a hypothetical person of ordinary skill in the
> art.

Applicants respectfully submit that if one follows the above guidelines and analyzes the art properly, that there is no suggestion of the invention as claimed.

4.   The Office Action rejected the claims under the inappropriate "obvious to try" standard.

Finally, the present rejection is basically an argument that it would be obvious to try or obvious to experiment with neural networks to arrive at a method for predicting efficiency of antisense oligonucleotides. "Obvious to experiment" or "obvious to try" is not a proper standard for making a determination under Section 103. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). The fact that Wu discusses using neural networks for analyzing ribosomal RNA phylogenies does not show obviousness of the present invention, because Wu does not suggest how that end might be accomplished. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 91 (Fed. Cir. 1986). Following the teachings of Wu, there would not be a reasonable expectation of success of making the present invention. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 U.S.P.Q.2d 1016, 1022 (Fed. Cir. 1991); *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). If obvious to try was a proper standard for determining obviousness of an invention, then virtually no

inventions involving recombinant DNA methods or neural networks would be patentable because it is so often obvious to try to use them for inventions involving diagnostics, pharmaceuticals, genetics, and the like. For these reasons, it is respectfully submitted that the present invention is not obvious under § 103.

5. Response to Office Action's Response to Applicants' Previous Arguments

The Office Action cited *In re Keller*, 642, F.2d 413, 208 USPQ 871 (CCPA 1981), and *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986), for the proposition that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Regardless of whether or not these cases stand for the stated proposition, Applicants did not fail to attack the cited references in combination. Applicants stated what the cited references teach and then showed that the cited references, *either alone or in combination*, fail to teach each and every limitation of the claims. The response filed November 25, 2005, stated at page 35 (emphasis added): "*the combination of Matveeva and Wu fails to disclose or suggest each and every limitation of the presently claimed invention.*" Therefore, Applicants attacked

the *combination* of Matveeva and Wu, and the Office Action's comment relating to attacking references individually is moot.

With respect to the motivation to combine references, the Office Action referred to Matveeva as being a step toward being able to predict antisense activity in cells using simplified model systems and that data, such as was analyzed in Matveeva, must be obtained and further analyzed with statistical methods for future practical use of such assays. The Office Action further quoted Wu wherein it was stated that neural networks compare favorably to other methods, such as Fasta and Blast, for phylogenetic classification of rRNA sequences. Applicants respectfully submit that these statements from the cited references do not teach, suggest, or motivate a person skilled in the art to arrive at the presently claimed invention. Matveeva suggests using simplified model systems and statistics for predicting antisense activity in cells. But, as acknowledged in the Office Action, Matveeva does not teach, suggest, or motivate a person to use neural networks for such an end. Wu suggests using neural networks for phylogenetic classification of rRNA. This suggestion does not teach, suggest, or motivate a person skilled in the art to use neural networks for non-phylogenetic-classification analysis, namely, structure/function correlations of oligonucleotides for antisense activity in cells.

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Finally, the Office Action alleged that "applicant's

arguments fail to comply with 37 CFR 1.111(b) because they amount

to a general allegation that the claims define a patentable

invention without specifically pointing out how the language of

the claims patentably distinguishes them from the references."

This is incorrect. At pages 35-36 of the response filed November

25, 2005, Applicants stated:

> Still further, the combination of Matveeva and Wu fails
> to disclose or suggest each and every limitation of the
> presently claimed invention. For example, the cited
> references fail to disclose or suggest (1) mapping
> sequence motifs of a preselected length found in the
> sequence data contained in the database, entering
> counts for each of the sequence motifs in selected
> input nodes of the input layer, and entering activity
> data correlated with the counts of the sequence motifs,
> (2) training the artificial neural network having the
> counts entered in the input layer such that the
> artificial neural network produces an output in the
> output layer upon entry of sequence motif counts,
> wherein the output comprises a measure of predicted
> activity correlated with sequence motif counts for a
> test oligonucleotide, (3) mapping sequence motifs of
> the preselected length present in a nucleotide sequence
> of a test oligonucleotide complementary to at least a
> portion of the selected RNA, determining counts of the
> mapped sequence motifs, and entering counts of the
> sequence motifs present in the nucleotide sequence of
> the test oligonucleotide in the input layer of the
> artificial neural network, and (4) obtaining output of
> the predicted antisense activity of the test
> oligonucleotide for down-regulating expression of the
> selected RNA. For this reason, a *prima facie* case of
> obviousness has not been established.

This portion of the response specifically lists four specific

ways that the language of the claims distinguishes them from the

cited references.   Therefore, the allegation that Applicants

failed to comply with 37 CFR 1.111(b) is simply not true.

Applicants did indeed specifically point out four limitations of

the claims that are not found in the combination of the cited

references.   Applicants respectfully submit that the deficiencies

of the cited references should be recognized, and the rejection

based on Section 103(a) should be withdrawn.

6.   Conclusion

For all of the reasons set out above, it is respectfully

submitted that a *prima facie* case of obviousness has not been

established with respect to the presently claimed invention.

Therefore, withdrawal of the rejection is respectfully requested.

VI.   Conclusion

Should the Examiner deem it advisable to conduct a telephone

interview for any reason, the undersigned attorney would be most

agreeable to receiving a telephone call to expedite the

prosecution of the application.

For the reasons given above, Applicants respectfully request

reconsideration and allowance of Claims 1, 2, 4, 8, 10, 12, 13,

17, 18, 20, 22, 23, 25, 29, 31, 33, 34, 38, 39, 41, 43, 65, and

66 and passage of this application to issue.

DATED this _17th_ day of July, 2006.

Respectfully submitted,

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